Ethnomedicinal, Pharmacological and Phytochemical Screening of Supari (Areca catechu Linn.): A Review

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Abstract
Supari (Areca catechu Linn.) is a tall tree about 10–20 m long. It is used both locally and internally. Local application is beneficial in various acute inflammatory conditions in the form of gargle, vaginal douche or abzan, decoction, juice and oil. Internally it act as muqavvi-e-qalb (cardiotonic) and muqavvi-e-ama (intestinal tonic), sozish media (gastric irritation), dries the excessive secretions of mouth, used in vomiting and nausea, strengthen the teeth and gums, excrete the bilious matter; bark powder expels intestinal worms, jiryan (nocturnal emission). It is also used in the treatment of ishaal (diarrhoea), saulan-ur-rehm (leucorrhoea), khurooj rahem wa miqad (prolapse of uterus and anus) in oral powder dosage form. Ethnobotanical actions have also been discussed which narrates the action of this magic medicine in different dosage forms. It possess various pharmacological activities such as antiplatelet activity, memory enhancing activity, antinociceptive activity, anti-allergic activity, hepatoprotective activity, anti-inflammatory activity and antimalanogenesis activity, antifertility activity, anti-ovulatory activity, anti-diabetic activity, wound healing activity, anti-oxidative activity, free radical scavenging activity, antiyaluronidase activity, anti-aging activity, antilcerogenic activity, antinfective study, radioactivity reducing activity in blood, cytoxicity activity, carcinogenic and toxicity study which has been scientifically evaluated by various studies have been discussed in this paper. Phytochemical studies done so far are also been discussed but isolation of various new structures can make the drug worldwide accepted. This article is an overview of plant morphology, phytochemical studies done on different parts of Supari, biochemical compounds as functionally active molecules, action and uses of Supari claimed by Unani medicine, therapeutic effects studied all over the world, and pharmacological studies scientifically proven yet. Further studies should be done to know the underlying mechanisms and type of biochemical compounds involved in these beneficial effect.

Keywords: Supari (Areca catechu), Unani, phytochemical, ethnomedicinal, pharmacological

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INTRODUCTION
Areca catechu Linn. comes under the list introduced by Arabs in their Materia Medica which is compiled from Ibn-i-Baitar’s Jame-ul-mufradat [1]. Areca commonly known as betel nut palm or areca palm is slender, single trunked, tall palm grows up to 30 m height. The name areca, means "cavalier", may be derived from the Kanarese word adeke or the Malayalam adakka. The first description of this tree dates back to that of Herodotus (ca. 340 B.C.E.). Later, both the palm and the chewing of the betel were more or less precisely discussed by many Arabic and European travellers e.g., Abdullah Ibn Ahmad, Marco Polo, Vasco De Gamma, Garcia De Orta etc in their travel reports. Betel nut is mentioned in Chinese works written before the Christian era under the name Pin lang, by some supposed to be a corruption of the Malay name pinang [2]. A mature tree in full bearing can have inflorescences containing up to 644 female and 15–48,000 male flowers. The male flowers open first. Their sweet scent attracts honeybees and other insects, but these insects do not frequent the female flowers and thus their role as pollinators is doubtful. Several days after the last male flower is shed, the female flowers open. They are fertilized by pollen that is wind transported from
neighbouring trees. Seasonality of flowering depends on location such as in Malaysia the palms flower year round; in India they flower from November to February. No data are recorded on seasonality of flowering in the pacific [3]. It possesses various pharmacological activities.

**TAXONOMY [4]**

| Kingdom: | Plantae |
| Order: | Arecales |
| Family: | Areaceae |
| Subfamily | Arecoideae |
| Genus: | Areca |
| Species: | catechu |

**Botanical Name [4]:** Areca catechu Linn.

**VERNACLAR NAMES [5, 6]**

**Arabic:** Fofal, Fufal.

**English:** Areca nut or betel nut palm, areca palm, pinang palm, catechu palm, catechu tree, drunken tree, supari palm, adike, arbor areka, areca, areca nut palm, areca nut tree, areka palm, arequero.

**Hindi:** Supari, Chaalia, Adike, Poogi phalam, Adakka, Surattu supray.

**Persian:** Pupal, Popal, Girdchob, Pinang.

**Sanskrit:** Kramuka, Ghonta, Akota, Chataphata, Chikkana, Dirgha padapa (an elongated tree), Dridha valkala (with a firm bark), Ghonta, Gopadala, Guvaka, Kapitana, Khatpura, Kra-Muka, Puga, Pugi, Raja Tala (the royal tala), Suranjana, Tambula, Tantu sara (fibrous fruit), Puwak, Pyan, Pyanbaum, Sopariand Valkataru, Puwak, Pyan, Pyanbaum, Sopari.

**Urdu:** Chhaliya, Supari.

**PLANT DESCRIPTION (MAHIYAT)**

It is a tall tree of 10–30 m height with a trunk 25–30 cm in diameter and long stem standing or hanging like coconut tree. Leaves are like coconut leaves but somewhat smaller and thinner. Leaves are even pinnately compound 1–1.5 m long, pinnae 30–50, lanceolate. Flowers are unisexual with both male and female flowers born in same inflorescence.

It is very sensitive to sunlight so grow in shade. Tree is thorn free. The gum obtained from this tree is a good substitute of mocharas. Fruits appear in bunches like dates but are smaller in size. Raw seeds have very astringent taste (baksa). Stem is green that turns red and then black after drying. After full ripening, the bunch gets separated and fruits are collected and boiled in water and coverings are separated. Finally obtained kernel is supari (chhaliya). Four types of supari are mentioned in the Unani classical text: 1. Reddish black coloured, conical in shape, baksa (astringent) and some talkh (bitter) in taste, this type is added in dentrifices (sanoon). 2. Teerah in colour, flat in appearance and less baksa (astringent) in taste that is called as chikni supari, commonly eaten along with paan (betel). 3. Red coloured from outside and white from inside, bigger in size, is called supari chhaaliya. It is also commonly eaten along with paan (betel). 4. Khapriya supari: Conical shape, long, soft, slippery/smooth and taste like coconut. Commonly available supari is reddish white, slippery, this is called barrah supari, it is further divided into two types one is smaller and conical shape known as maanikchandi and another is bigger in size and flat in shape called as jahazli [7]. It is of two types and best one is weighty and solid [8].

**HABITAT**

Native to Philippines however cultivated in China, Indonesia, Malaysia. Exotic range is cultivated in Fiji, India, Japan, Kenya, Madagascar, Pakistan, Papua New Guinea, Samoa, Solomon Islands, Sri Lanka, Tanzania etc. [9]. In India it is cultivated in coastal regions of Western Ghats, Assam and southern regions such as Mysore, Hyderabad, etc. [7].

**PARTS USED MEDICINALLY:** Nuts, flower, leaves, bark [7, 10] and root [10].

**MIZAJ (TEMPERAMENT):** Cold and Dry 2°C or 3°C [7] Cold 2°C Dry 3°C [11]; Cold 2°C Dry 2°C; Cold 2°C Dry 2°C.

**AFAAL (FUNCTIONS)**

Supari (nut) and its flower (Gule Supari) are mushtahi (appetizer), cures balghami (phlegmatic), safrai (bilious) and sawda (black bile) diseases, qabiz (astringent) for oral secretions, muqavvie asnan wa lissa (strengthen the teeth and gums), musakkin-e-hararat (febrifuge) [7], mudire boul (diuretic) [7, 13], habisuddam (haemostatic), nafe sailan rehm (cures leucorrhea) [14], Raada mawad,


muqavvi-e-galb (cardiotonic), muqavvi-e-baah (aphrodisiac), muhallile waram (anti inflammatory) [14], qabiz (constipative), and rade [8]. Nut is used as an astringent, stimulant and antihelminthic in China, Indo China, the Malay Archipelago, Australia, Melanesia, and Madagascar [9].

DAWAII ISTEMAL (THERAPEUTIC USE)
Its local application (tila) is beneficial in intafakh (catarrhal conjunctivitis) and tarfa (haemorrhagic conjunctivitis) and other acute inflammatory conditions. It also removes foul smell of mouth and cures stomatitis and strengthens the teeth. It tones up the prolapsed or loose organs. It is useful in nonhealing ulcer, gangrene and plague so it is added in taryaq as an ingredient [8]. Sprinkling of its powder is beneficial in syphilitic ulcer. Gargle with water obtained from its tree called as sataari or tadi have sard khushk mizaj which strengthens the teeth, tone of stomach, if used as vaginal douche or abzani; it tightens the vagina and closes the os. Its decoction or poultice is also used to reduce inflammatory conditions. Application of ash of supari along with badi elaihi is beneficial in oral stomatitis. Massage with its leave juice and oil is beneficial in wajaul zuhr asbi (nervine back pain) [7].

Internally it acts as cardiotonic and increases the vital capacity of lungs [8]. Powdered supari and haldi with sugar is beneficial in vomiting. Chewing of supari, longekattha and chuna in paan stops the matli (nausea) and act as muqavvi-e-ama (intestinal tonic). Supari boiled in alcohol cleans the mouth and prevents the sozish meda (gastric irritation). It dries the excessive secretions of mouth, strengthens the teeth and gums. Its flower juice with paan excretes the bilious matter. Bark powder expels intestinal worms. Bark of supari and kher with honey are beneficial in jiryan [7]. Due to its qabiz (astringent) properties it is used in ishaal (diarrhoea), sailaanurrehm (leucorrhoea), jiryan, khurooje rahem wa miqad (prolapse of uterus and anus) as oral powder [11].

MUZARRAT (ADVERSE EFFECTS)
Mujaffij (dessicant) [11], mukhashin sadar (chest irritant) [7], muzir riya (dangerous for lungs) [8], khafqan (palpitation), sudaa (headache), qoolanj gulan (colitis) [12], sang gurda wa masana (urinary bladder calculus) [7].

MUSLEH (CORRECTIVE):
Roghbanbadam (Prunus dulcis oil), nabat safaid (sugar) [11], gondbabool (Acacia nilotica) for lungs and Kateera (Acacia arabica) [12] for all conditions [7].

BADAL (SUBSTITUTE): Sandulsurkh (Pterocarpus santalinus) or kishneez khushk (Coriandrum sativum) half quantity to supari [7, 12].

MUQDAR-E-KHURAQ (DOSE): 3–5 g [7], half darham [8].


PHYTOCHEMICAL CONSTITUENTS
Areca nut palm and its various parts are extensively evaluated for its phytochemical constituents—Polyphenol (20%), fat (15%), starch (20%) and alkaloids (0.5%). The polyphenol, mostly flavonols, include about 10% of (+) catechin, 2.5% epicatechin, 12% (+) leucocyanidin, the remaining portion being complex flavonoids in varying degrees of polymerization. A series of dimeric, trimeric, and tetrameric procyanidins has been isolated from seeds of Areca catechu L.

Several alkaloids are cainine, arecaine, arecolidine, arecoline, guavacine, guavacoline and choline have been isolated from the nut of Areca catechu L. [15].

Mineral Content
It includes calcium (0.05%), phosphorus (0.13%) and iron (1.5 mg/100 g). It also contains vitamin B6 (286.9 mg) and vitamin C (416.2 mg). Seeds of Areca nut also contain tannins, gallic acid, fat, and gum [16].

The chief component Areca nut fatty acid are lauric acid (19.5%), myristic acid (46.2%) and palmitic acid (12.7%), and in the unsaturated
portion oleic acid (6.2%), linoleic acid (5.4%) and hexadecenoic acid (7.2%). Minor proportions of stearic acid, decanoic acid and of unsaturated monoethylenic C₁₂ and C₁₄ acids are also present. The chief components glycerides are trimyristin, dimyristins and lauromyristopalmitin; hexadecenolaurymyristin with some oleo-(linoleo)myristopalmitins and dimyristins; 14% of diunsaturated-monsoaturated (oleolinoleoglycerides, mostly oleolinoleopalmitin) [17]. New 5’-nucleotidase inhibitors named NF-86I, NF-86II were also isolated from the seeds of Areca catechu L. [18].

ETHNO MEDICINAL ACTIONS

- Nuts (250 g) are powdered and boiled in 2 l of cow milk. To this 5 g kesar and ilaychi are added and again boiled until it gets solidified (supari pag) [19].
- Juice of tender leaves is mixed with oil externally applied to Lumbago [10].
- Leaves are used in bronchial troubles and cough [10].
- Young green shoots are used as abortifacient in early pregnancy [10].
- Decoction of root is used in liver disorder and sore lips [10].
- Bark deobstruent is used in dropsy and flatulences [10].
- The nuts are used in diarrhoea, ulcers, anthelmintic and its paste as dentifrice [10].
- The powdered nut in doses of 10 or 15 grains every three or four hours is useful in checking diarrhoea arising from debility. It has also been found very useful in urinary disorders and is reported to possess aphrodisiac properties. The dried nuts when chewed produce stimulating and exhilarant effects on the system.
- The nut is regarded as a nervine tonic and emmenagogue and is used as an astringent lotion for the eyes.
- The young nut possesses astringent properties and is prescribed in bowel complaints and bad ulcers.
- The juice of young tender leaves mixed with oil is applied as an embrocation in cases of lumbago, and a decoction of the root is a reputed cure for sore lips.
- The nut is used as an astringent for bleeding gums, women employ it both internally and locally for stopping watery discharges from the vagina.
- The grated nut is given as an anthelmintic for roundworms and tapeworms.
- In Ceylon, the nut is scraped and applied externally to ulcers; it also strengthens the gums and is given for worms in animals.
- In Malaya, the green fruit in its unripe state is sometimes used as a poison in combination with opium. Malay women use the young green shoots as an abortifacient in early pregnancy.
- In China, the nuts are used for their tonic, astringent and anthelmintic properties. In some parts of China the nuts bruised and powdered are mixed with the green food given to horses, and they are thus considered a preventive agent against diarrhoea. In the north of China, small pieces are boiled and decoction is taken as a domestic remedy in various visceral affections.
- In Cambodia the leaves are used internally for bronchitis and externally for Lumbago, the fruit is given in diarrhoea in combination with opium and the root is prescribed in diseases of the liver.
- The juice of the tender nuts acts in small doses as a laxative.
- The nut has no anthelmintic value. It is not an antidote to either snake venom or Scorpion venom.
- Areca nut is commonly used for skin ulcers in Indian traditional medicine. Areca nut oil is prepared and applied topically for burn wound healing.
- Nut is aphrodisiac, useful in urinary disorders, astringent, anthelmintic, nervine tonic, in veterinary medicine as vermifuge for tapeworm in snakebite.
- Betel chewing has been claimed to produce a sense of well-being, euphoria, heightened alertness, sweating, salivation, a hot sensation in the body and increased capacity to work.
- Arecoline was used in veterinary medicine in the treatment of cestodes in dogs. Oral administration causes paralysis of the worms and catharsis, so the worms are expelled alive and intact.
• Areca catechu L. is a common traditional Chinese medicinal plant used to treat dyspepsia, constipation, beriberi and oedema.
• In traditional Chinese medicine, Areca catechu seed is commonly used for treatment of various diseases such as dyspepsia, constipation, beriberi and oedema [19].
• A slice of betel nut is mixed with part of a leaf from the Piper betel vine and a piece of lime, plus cloves, nutmeg, tamarind, turmeric, cardamom, and sometimes resins, then placed in the mouth and chewed or sucked on for hours [20].

MECHANISM OF ACTION [21]
• Pharmacologically the action of arecoline very much resembles that of muscarine, pallerterine and pilocarpine all of which are violent stimulants of the parasympathetic nervous system. They stimulate the intestine, constrict the bronchi, decrease the heart rate and lower blood pressure. Arecoline also stimulates salivation and decreases sweating. The nut is used medicinally in various forms, as powders (in dosage of 10–30 g), fluid extracts (doses of 10–30 minims) and tinctures (1 to 2 drachms). Arecoline hydrobromide is a statutory drug in the Indian, British, German and French pharmacopias. Taenine is a preparation containing Areca nut extract, forming a liquid medicine used in veterinary practices against tape worms. The advised dosage of this medicine for a dog is one minim for every pound of body weight.
• It violently stimulates the peristaltic movements of the intestines and bowels. It produces a marked constriction of bronchial smooth muscle which can be overcome by adrenaline and atropine. When dropped into the eye, 1% solution constricts the pupil like physostigmine. It is a powerful sialagogue, and stimulates the secretion of sweat in the same way as pilocarpine. The mutagenicity of betel quid, arecoline (the main alkaloid in Areca nut), arecaidine (a metabolite of arecoline) and N-nitrosoguacoline has been reported.

PHARMACOLOGICAL STUDIES
Some important researches carried out on various parts of this plant are as follows:
1. Absorption Lowering Activity of Intestinal Free Cholesterol: Park et al. studied strong inhibitory activity against pancreatic cholesterol esterase (pCEase) in vitro which was found to lower the absorption of dietary cholesterol ester. Male rats were fed a diet containing free cholesterol (1%, w/w) either with or without an Areca nut extract supplement (0.5%, w/w). The Areca extract supplement significantly lowered the plasma cholesterol concentration by 25% without any change in the plasma triglyceride concentration, when compared to the control group. The supplement also significantly lowered the small intestinal pCEase activity by 39.1% compared to that of the control group [22].
   Another study for inhibitory activity on triglyceride absorption and cholesterol metabolism was performed to determine whether Areca extracts also exert an inhibitory activity on triglyceride absorption in triglyceride-fed rats. Male rats were fed a diet containing corn oil (10%, w/w) with or without an Areca nut extract supplement (0.5%, w/w). The supplementation of Areca extract significantly lowered the absorption of triglyceride and the plasma lipid concentration. The absorbed triglyceride that appeared in the blood after an oral dose of [9, 10(n)-(3)H] triglyceride was significantly lower in the rats supplemented with the Areca nut extract, compared with the control group [23].
2. Cholesterol Regulating Enzyme Activity: The effects of naringenin and its synthetic derivative, naringenin 7-O-cetyl ether, on the lipid profile, the cholesterol-regulating enzyme activity and the excretion of sterol were compared in rats fed a high-cholesterol (1% wt/wt) diet. The results suggested that cholesterol biosynthesis and esterification were concomitantly reduced by 2%, as indicated by the decreased HMG-CoA reductase and ACAT activities [24].
3. Memory Enhancing Activity: Joshi et al. evaluated the effect of Areca catechu
Linn. extract on learning and memory in rats using radial arm maze. Two types of extract namely, wet and dried *Areca catechu* were used. Three groups of rats each consisting of seven animals were used. Test groups were given 500 mg/kg p.o. of wet *Areca catechu* extract and dried *Areca catechu* L. extract, respectively. Hence increase in spatial memory could be because of higher amount of arecoline present in wet *Areca catechu* L. extract in comparison to the control group of rats [25].

4. **Dependency Syndrome Study**: Mirza *et al.* conducted an observational cross-sectional study on healthy individuals, who were users of any one of the three products (*Areca* nut only, *Areca* nut with tobacco additives, cigarette smokers) by convenience sampling of people coming to hospital to seek a free oral check-up. Final analysis was done on 851 individuals, of which 36.8% (n = 314) were *Areca* nut users, 28.4% (n = 242) were the chewers of *Areca* with tobacco additives and 34.7% (n = 295) were regular cigarette smokers. Multivariate analyses showed that individuals using *Areca* nut with tobacco additives were significantly more likely to have dependency syndrome (OR = 2.17, 95% CI 1.39–3.40) while cigarette smokers were eight times more likely to have dependency syndrome as compared to *Areca* nut only users [26].

5. **Antinociceptive Activity**: Barman *et al.* evaluated the antinociceptive effect of crude methanol extracts of stems and leaves of *Areca catechu* L. in acetic acid-induced gastric pain writhing model in Swiss albino mice. The methanol extract of *Areca catechu* stems dose dependently reduced the number of (constrictions) in mice, when tested at doses of 50, 100, 200, and 400 mg extract administered per kg body weight. Significant reductions in the number of writhings were noted with all administered doses. At even the lowest dose of 50 mg extract per kg body weight, the antinociceptive activity of leaf extract was comparable to that of 400 mg aspirin per kg body weight [27].

6. **Hypertensive Activity**: A population-based prospective analysis was done on 19934 Bangladeshi adults in rural area of Bangladesh. At baseline, betel quid was chewed by 33.2% of the cohort (35.5% of men, 31.6% of women). In a subsample in which we collected methods of use, 17.5% chewed it without tobacco and 82.5% chewed it with tobacco. At follow-up, persons who chewed betel quid without tobacco had higher systolic blood pressure, diastolic blood pressure and arterial pressure in comparison with never users. After controlling for other explanatory variables, chewing betel quid without tobacco was associated with general hypertension [28].

7. **Oral Cancer**: It was found that there is relationship between betel quid or *Areca* nut chewing habit and oral cancer. A number of investigators have been able to produce cellular changes such as leukoplakia by application of betel quid or *Areca* nut extract to the buccal mucosa of different animal [29].

8. **Cardiovascular Risk**: Chin-Hsiao Tseng investigated the association between betel nut chewing and subclinical ischemic heart disease (IHD) in Taiwanese type 2 diabetic patients. A total of 394 male patients aged ≥45 years and without previous heart disease were studied of which 349 had no habit of chewing betel nut and 45 possessed the habit for ≥5 years. Subclinical IHD was diagnosed by a Minnesota-coded resting electrocardiogram and was present in 71 cases [30]. Iqbal *et al.* investigated the effects of two dosages of betel nut on homocysteine, inflammation and some of the components of metabolic syndrome, such as hypertriglyceridemia, low HDL-cholesterol, obesity and fasting hyperglycemia in a rat model. Thirty-six adult female Sprague Dawley rats, aged 10–12 weeks were divided into three equal groups. Betel nut ingestion had no effect on the mean body weights of rats. Low dosage of betel nut is found to be associated with hypercholesterolemia. So it can be said that, betel nut ingestion is not associated with hyperhomocysteinemia, hypertriglyceridemia, hyperglycemia,
inflammation and increase in body weight in a rat model [31].

9. **Antibacterial Activity in Dental Caries:** Sumitra studied that dental caries prevention by traditional medicines, fatty acids (myristic and oleic acids, etc.) and procyanidins from betel nuts (the seed of *Areca catechu* L.) were respectively revealed to be the major antibacterial principles against a primary cariogenic bacterium, *Streptococcus mutans*, and the major inhibitory principles against glucosyltransferase from *S. mutans* [32].

10. **Antiplatelet Activity:** Ghayur investigated the mechanism and the compound(s) responsible for antiplatelet and acetylcholinesterase (AChE) inhibitory effects of Aqueous–methanol (70%) *Areca catechu* (betel nut) crude extract (Ac.Cr). Antiplatelet activity was measured in human platelet-rich plasma by using a Lumi-aggregometer while anti-AChE activity was measured spectrophotometrically in vitro. Out of the tested compounds, none of the compounds in betel nut showed any antiplatelet effect except for catechin that was the most potent against epinephrine-induced aggregation. Catechin was significantly less potent than Ac.Cr, indicating a presence of additional compound(s) with antiplatelet activity. For the AChE inhibitory effect, only tannic acid, gallic acid, diosgenin and isoguvacine were found to be active, whereby tannic acid was more potent than Ac.Cr. The study showed the possible antiplatelet and AChE inhibitory potential of betel nut [33].

11. **Anti-aging Activity:** The anti-aging effect of *Areca catechu* L. extract (CC-516) on skin were investigated both in vitro and in vivo. The CC-516 is composed of a relatively high amount of protein (26%) and carbohydrate (37.5%), and it has a high proportion of proline (13%) of free amino acid content. The inhibitory effect of CC-516 on elastase exhibited a 37–98% inhibition for a 10–500 tng/ml concentration, and IC50 values of 40.8 tng/ml for porcine pancreatic elastase (PPE) and 48.1 lag/ml for human leukocyte elastase (HLE), respectively. The treatment with CC-516 improved skin hydration, skin elasticity, and wrinkle reduction [34].

12. **Stability Assessment for Cosmetic Applications:** Stability of raw betel nut seed was investigated for its application in cosmetic products. The betel nut seed extract 95% ethanol extraction with microwave assistance. The pH of all extracts tends to decrease after 56 days of storage, while the color change, slightly increased. It has been found that the EPC and antioxidant capacity of the extract were most stable at pH 4–6 and 8–10, especially when storing at low temperature. The study showed high stability of betel nut seed extract [35].

13. **Antimicrobial Study:** de Miranda et al. investigated the effect on the growth of salivary and selected oral microorganisms of Areca nut, aqueous extracts of the nut, its major alkaloid arecoline and the components tannic acid and catechin of its tannin fraction. The antibacterial properties of the above were tested on *Streptococcus mutans*, *Streptococcus salivarius*, *Candida albicans* and *Fusobacterium nucleatum* and, as a control, *Staphylococcus aureus*. This was followed by investigating its effect on salivary organisms cultured from the saliva after chewing boiled Areca nut. It was concluded that the hydrolysable tannins in the tannin fraction, which include tannic acid, are responsible for the antibacterial properties of nut and that prolonged intraoral exposure to the nut can suppress bacteria in the mouth [36].

14. **Anti-inflammatory and Anti-melanogenesis:** Topical application of Areca nut extract inhibits hyaluronidase activity in vivo on delayed hypersensitivity and croton-oil induced ear oedema in mice. The results suggested that Areca nut extract may reduce immune-regulatory/inflammatory action on skin problem. Skin whitening effect of Areca nut extract showed thorough inhibitory activity on mushroom tyrosinase activity and melanin synthesis in b16 melanoma cells. This study indicated that Areca nut extract was an effective anti-inflammatory/anti-melanogenesis agent and can be used as a new agent for cosmetics [37].
15. Anti-oxidative Activity: Ethanolic extract (CC-516) from *Areca catechu* L. was prepared and its various biological activities were evaluated. CC-516 showed potent anti-oxidative, free radical scavenging, and antiyalurondase activity. Anti-oxidative effect of CC-516 (IC₅₀: 45.4 µg/ml) was lower than butylated hydroxytoluene (IC₅₀: 5 µg/ml), but similar to tocopherol and higher than ascorbic acid [38]. In another study, Lin and Li evaluated the antioxidant capacities of *Areca* flower extracts by using superoxide radical scavenging activity and reducing power; total phenolic content and total flavonoid content were also detected. In all the tested models, the *Areca* flower extracts showed their ability to scavenge superoxide radical and reducing Power in a dose-dependent manner. The distilled water (afw) extract had higher superoxide radical scavenging activity and reducing power than of distilled water/methanol (afm) extract [39].

Arulpriya and Lalitha also studied antioxidant activity by testing three different extracts (acetone, ethyl alcohol and aqueous) of the aerial roots of *Pothos aurea* intertwined over *Areca catechu* (mp) were carried out by two different methods namely 1, 1-diphenyl-2-picryl hydrazyl (DPPH) radical scavenging assay and reducing power test. Higher antioxidant potential of the extracts was observed in both DPPH scavenging and reducing power assay [40].

Toprasri *et al*. have done Comet assay to test antioxidative effects of extracts from different parts of *Areca catechu* L. Effects of aqueous and various organic extracts of different parts of this plant on oxidative DNA damage in Human hepatocarcinoma hepg2 cells was compared with butylated hydroxytoluene (bht) using the comet assay. Hydrogen peroxide was used as DNA damage inducing agent. Comparison of a series of organic extracts from the *Areca* seed and nut husk of this plant was performed. Methanolic and methylene chloride extracts of *Areca catechu* nut husk exerted antioxidant activity while extracts of other parts, e.g., seed, leaf bud, flower bud and bloomed flower, did not [41].

Three methods widely employed in the evaluation of antioxidant activity, namely 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method, static headspace gas chromatography (HS-GC) and beta-carotene bleaching test (BCBT), have been compared with regard to their application in the screening of plant extracts. Being rapid, simple and independent of sample polarity, the DPPH method is very convenient for the quick screening of many samples for radical scavenging activity [42].

In another study, antioxidant activity testing of three different extracts (acetone, ethyl alcohol and aqueous) of the aerial roots of *pothos aurea* intertwined over on *Areca catechu* (mp) were carried out by two different methods namely 1, 1-diphenyl-2-picryl hydrazyl (DPPH) radical scavenging assay and reducing power test. Higher antioxidant potential of the extracts was observed in both DPPH scavenging and reducing power assay.

In *vitro* antioxidant activity by optimization of the ultrasound-assisted extraction technology for total phenol from betel (*Areca catechu* l.) nut seed was carried out. The predicted value and measured value of total phenol was 164.74 mg catechin equivalents/g of betel nut seed (mg ce/g bns) and 160.95 mg ce/g bns under this condition, respectively. The experiments of antioxidant activity showed that the betel nut seed extract presents strong antioxidant activities to the DPPH and ABTS radical and the ec50 was 113.42 and 105.69 µg/ml, respectively [43].

16. Antihyaluronidase Anti-allergic and Anticytotoxicity Activity: CC-516 inhibited effectively hyaluronidase activity (IC₅₀: 416 µg/ml), showed inhibition *in vivo* on delayed hypersensitivity as well as croton-oil induced ear oedema in mice when it was topically applied. These results strongly suggested that CC-516 may reduce immuno regulatory/inflammatory skin trouble. Also, from the results, we have elucidated that CC-516 showed anti-allergic and
anticytotoxicity activity. The whitening effect of CC-516 shown by the inhibition of mushroom tyrosinase activity with IC 50 of 0.48 mg/ml and of melanin synthesis in B16 melanoma cells. This study indicated that CC-516 is effective in anti-inflammatory/antimelanogenesis, and can be used as a new agent for cosmetics [44].

17. Regenerative Activity: Owing to its muscarinic and nicotinic agonist properties, arecoline has shown improvement in the learning ability among animal. Arecoline administered via i.v. route did indeed show modest verbal and spatial memory improvement in Alzheimer’s patients, though due to arecoline’s possible carcinogenic properties [45].

18. Hepatoprotective Activity: Aqueous extracts from seeds of Areca catechu L. (Areaceae) was investigated for their hepatoprotective potential by studying antioxidant capacity using four different methods, by determining their in vitro anti-inflammatory activity against 5-lipoxygenase, and by evaluating their hepatoprotective potential against liver injury induced by carbon tetrachloride (CCL4) in rats. Areca catechu extracts exhibited potent antioxidant and anti-inflammatory activities. Treatment of rats with Areca catechu extract reversed oxidative damage in hepatic tissues induced by CCL4. It was suggested that extracts rich in either condensed or hydrolysable tannins and known for their potent antioxidant and anti-inflammatory activities, may potentially confer protection against oxidative stress-induced liver injury [46].

19. Carcinogenic and Toxicity Study: The study was for in vivo and in situ effects of aqueous and alcoholic extracts of Areca nut on rat intestinal epithelial cell membrane. Significant declines in brush border membrane alkaline phosphatase, Ca2+-Mg2+-ATPase, and the digestive enzyme sucrase. All findings suggested that prolonged chewing of Areca nut causes significant alterations in intestinal epithelial cell lining functions and could lead to malabsorption of nutrients [47].

20. Apoptosis Activity: Coordinated intracellular protein degradation mediated by the ubiquitin–proteasome pathway is crucial to a vast array of cellular processes including orderly progression through the mitotic cycle. Ubiquitin–proteasome system itself plays an important role in apoptosis, and some of the cellular pathways that are impacted upon by the proteasome, and may lead to apoptosis, are beginning to be dissected [48].

21. Antifertility Activity: The study evaluated the antifertility activity of Areca catechu L. in male albino rats. Alcoholic extract of Areca catechu was studied for antifertility activity at doses 300 and 600 mg/kg body weight. Fertility was assessed with mating test. Body weight and weight of the reproductive organs (testis and epididymis) were observed. Alcoholic extract of Areca catechu showed antifertility activity at 300 and 600 mg/kg body weight doses [49].

22. Antidiabetic Activity: It was done to evaluate anti diabetic activity of petroleum ether, chloroform and methanol extracts of Areca catechu L. leaf in Wister rats. Diabetes mellitus was induced in rats by single intraperitoneal injection of streptozotocin (STZ, 50 mg/kg body weight). After STZ induction the hyperglycemic rats were treated with all three extracts orally at the dose 200 mg/kg body weight daily for 15 days. Glibenclamide (0.5 mg/kg) was used as reference drug. The fasting blood glucose levels were measured on every 5th day during the 15 day treatment. All the extracts at 200 mg/kg orally significantly (p < 0.001) exhibited antidiabetic activity in STZ-induced diabetic rats by reducing and normalizing the elevated fasting blood glucose levels as compared to those of STZ control group. The methanol extract was most active. The study concluded that Areca catechu L. leaf confirmed promising antidiabetic activity in STZ-induced diabetic Wister rats [50].

23. Burn Wound Healing Activity: Verma et al. evaluated the burn wound healing property of Areca catechu L. kernel in normal as well as dexamethasone treated rats. Ethanolic extract of Areca catechu L.
kernel was prepared and an ointment was made with 2% of this extract. Burn wound was induced by standard procedure. Rats with burn wound model received either vehicle, standard drug or test drug. Test drug showed a significant reversal in wound contraction rate and epithelialization period in dexamethasone suppressed burn wound healing model. This study shown the wound healing property of Areca catechu L [51]. Azeez et al. also studied the wound healing profile of Areca catechu L. extracts on twelve-week-old healthy male Wistar rats weighing 150–200 g of three wound models were used. The study showed that the alkaloid of Areca catechu L. and polyphenols of it could be used to enhance the healing of burn wounds, leg ulcers and skin graft surgery [52].

24. Safety Assessment in Pregnancy: A retrospective cohort analysis of migrant and refugee pregnant women attending antenatal clinics along the Thai–Myanmar border was conducted by Chue et al. to examine the adverse effects of Areca nut use routinely recorded on enrolment of 7685 women, 2284 (29.7%) never used Areca or smoked (cheroots), 2484 (32.3%) only used Areca, 438 (5.7%) only smoked cheroots and 2479 (32.3%) used both Areca and cheroots. Pieces of ripe Areca nut in a leaf with lime, without tobacco, were used particularly among older multigravid women. Areca catechu L. related adverse pregnancy outcomes were not observed in this population, whereas smoking was clearly harmful [53].

25. In vitro Cytotoxicity Activity: Chetan et al. made an attempt to prove cytotoxic activity of various parts of medicinal plants including Areca catechu using MCF-7 and Vero cell line. Various parts of the medicinal plants were extracted by Soxhlet apparatus using solvents such as methanol and water. By trypan blue dye exclusion method, viability of MCF-7 and Vero cell lines were 85.50% and 81.13%, respectively. IC₅₀ value of methanol extract of aqueous extract of Areca catechu L. fruits were found to be 826.1 μg/ml by SRB assay and 1461 pg/ml by MTT assay, against MCF-7 cell line. From cytotoxicity study data by SRB and MTT assay, it was revealed that aqueous extract of Areca catechu L. are potent cytotoxic [54].

26. Central Nervous System Stimulant Activity: Betel nut may cause stimulant and euphoric effects. As a result, it is sometimes used for relaxation. Severe skin inflammatory reaction halted when transdermal device systemically deliver arecoline—a cholinergic—for use in managing neurological disorder in humans [55].

27. Molluscicidal Activity: In vivo and in vitro exposure of arecoline (the active component of Areca catechu seed) significantly inhibited the acetylcholinesterase (AChE), acid and alkaline phosphatase (ACP/ALP) activity in the nervous tissue. In another study, the increasing-effect components for molluscidates isolated from the dry nut of Areca catechu L. were studied. The results showed that arecoline was the most effective and it could decrease remarkably the amount of drugs when used together [56].

28. Ulcerogenic Activity: Al-bayaty et al. investigated the enhancement of ulcerogenic activity of ethanol extract from nuts of Areca catechu L. in ethanol-induced gastric mucosal injury in rats. Four groups of adult Sprague Dawley rats were orally pretreated, respectively with carboxymethyl cellulose (CMC) solution (ulcer control group), omeprazole 20 mg/kg (reference group), 250 and 500 mg/kg Areca catechu L. nut extract in CMC solution (experimental groups) one hour before oral administration of absolute ethanol to generate gastric mucosal injury. Histological studies of the gastric wall revealed that experimental groups exhibited comparatively severe damage of gastric mucosa; along with oedema and leucocytes infiltration of submucosal layer as compared to ulcer control group [57].

29. Antiulcerogenic Activity: Reena et al. evaluated the anti-ulcerogenic activity of aqueous extract of Areca catechu L. in ethanol-induced ulcer model in Sprague Dawley rats. For possible mechanism of anti-ulcerogenic potential, determination of...
ulcer index was done using the Merazzi-Uberti and Turba method. The study showed potential antiulcerogenic effect as compared to Ranitidine, which is the standard gastric antisecretory drug [58]. A workshop in Kuala Lumpur identified some lesions such as chewer's mucosa, Areca nut chewer's lesion, oral submucous fibrosis and other quid-related lesions. A new clinical entity, betel-quid lichenoid lesion, was also proposed to describe an oral lichen planus-like lesion associated with the betel quid habit [59].

30. **In vitro and in vivo Anti-allergic Activity:** The effects of various extracts from oriental medicinal herbs on mast cell-mediated allergic reactions have been investigated. Among the extracts, Arecae semen was the most potent inhibitor of antigen-induced degranulation in RBL-2H3 mast cells [60]. New 5'-nucleotidase inhibitors named NF-86I, NF-86II were recently isolated from the seeds of *Areca catechu* L. NF-86I and NF86II showed inhibitory effects on the growth of *Streptococcus mutans* MT8148(c) and *Streptococcus mutans* MT6715(g), respectively. In addition, these inhibitors could inhibit insoluble glucan formation from sucrose. Findings suggested that the 5'-nucleotidase inhibitors NF-86I and NF-86II may be useful antiplaque preventing agents [61].

31. **Parasympathomimetic Activity:** In the presence of lime, arecoline and guvacoline in Areca nut are hydrolyzed into arecaidine and guvacine, respectively, which are strong inhibitors of GABA uptake. *Piper betle* flower or leaf contains aromatic phenolic compounds which have been found to stimulate the release of catecholamines in vitro. Thus, betel chewing may affect parasympathetic, GABAnergic and sympathetic functions. Results suggested that betel chewing mainly affects the central and autonomic nervous systems [62].

32. **Reduced Radioactivity in Blood:** *Areca catechu* L. extracts exhibiting a strong inhibitory activity against pancreatic cholesterol esterase (pCEase) *in vitro* were previously found to lower the absorption of dietary cholesteryl ester. Male rats were fed a diet containing free cholesterol (1%, w/w) either with or without an Areca nut extract supplement (0.5%, w/w). The Areca extract supplement significantly lowered the plasma cholesterol concentration by 25% without any change in the plasma triglyceride concentration, when compared to the control group. Results suggested that the inhibition of intestinal ACAT and possibly pCEase may facilitate the metabolic efficiency of the Areca nut extract as regards the absorption of intestinal free cholesterol [64].

33. **Human Umbilical Vessels Relaxing Activity:** A study investigated the effects of arecoline—an active ingredient of the areca nut—on the tone of human umbilical arteries and veins and on the eNOS expression and cell proliferation of human umbilical vein endothelial cells (HUVECs). It was found that arecoline relaxes the human umbilical artery and vein rings in a concentration-dependent manner; the higher the concentration of arecoline, the greater the relaxation of the rings which suggest that long-term use or high doses of areca nut might induce endothelial dysfunction and associated diseases [65].

**Fig. 1:** Original Picture of Fresh Flower of Gule Fooral (*Areca catechu* Linn.).

**CONCLUSION**

This article is an overview of morphology, phytochemical studies done on different parts of Supari (*Areca catechu* Linn.), biochemical compounds as functionally active molecules,
action and uses as claimed by the Unani medicine, therapeutic effects studied all over the world, and pharmacological studies scientifically proven yet. Further studies should be done to know the underlying mechanisms and type of biochemical compounds involved in these beneficial effects.

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